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Application No: 10534348 Version No: 1.1

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<110> SILENCE, Karen
LAUWEREYS, Marc
DE HAARD, Hans

<120> SINGLE DOMAIN ANTIBODIES DIRECTED AGAINST TUMOUR NECROSIS FACTOR-ALPHA AND USES THEREFOR

<130> A0848.70005US00

<140> 10/534,348
<141> 2005-05-09

<150> PCT/BE03/00192
<151> 2003-11-07

<150> US 60/425073
<151> 2002-11-08

<150> US 60/425063
<151> 2002-11-08

<150> EP 03447005.4
<151> 2003-01-10

<150> PCT/EP03/06581
<151> 2003-06-23

<150> PCT/EP03/07313
<151> 2003-07-08

<160> 132

<170> PatentIn version 3.1

<210> 1

<211> 115

<212> PRT

<213> Lama glama

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Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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Ser Leu Arg Leu Ser Cys Ala Thr Ser Gly Phe Asp Phe Ser Val Ser
            20                  25                  30

Trp Met Tyr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Glu Ile Asn Thr Asn Gly Leu Ile Thr Lys Tyr Val Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asp Ser Leu Ile Pro Glu Asp Thr Ala Leu Tyr Tyr Cys
                85                  90                  95

Ala Arg Ser Pro Ser Gly Ser Phe Arg Gly Gln Gly Thr Gln Val Thr
            100                 105                 110

Val Ser Ser
        115
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<210> 2

<211> 121

<212> PRT

<213> Lama glama

<400> 2

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Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Phe Arg Val Asn
            20                  25                  30

Ala Met Gly Trp Tyr Arg Gln Val Pro Gly Asn Gln Arg Glu Phe Val
        35                  40                  45

Ala Ile Ile Thr Ser Gly Asp Asn Leu Asn Tyr Ala Asp Ala Val Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Thr Asp Asn Val Lys Lys Thr Val Tyr Leu
```

65 70 75 80

Gln Met Asn Val Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
85 90 95

Ala Ile Leu Gln Thr Ser Arg Trp Ser Ile Pro Ser Asn Tyr Trp Gly
100 105 110

Gln Gly Thr Gln Val Thr Val Ser Ser
115 120

<210> 3

<211> 123

<212> PRT

<213> Lama glama

<400> 3

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Thr Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Trp Met Tyr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Thr Val Asn Thr Asn Gly Leu Ile Thr Arg Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Tyr Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Lys Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Lys Val Val Pro Pro Tyr Ser Asp Asp Ser Arg Thr Asn Ala Asp
100 105 110

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
115 120

<210> 4

<211> 129

<212> PRT

<213> Lama glama

<400> 4

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Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Asp His
            20                  25                  30

Ser Gly Tyr Thr Tyr Thr Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys
        35                  40                  45

Glu Arg Glu Phe Val Ala Arg Ile Tyr Trp Ser Ser Gly Asn Thr Tyr
    50                  55                  60

Tyr Ala Asp Ser Val Lys Gly Arg Phe Ala Ile Ser Arg Asp Ile Ala
65                  70                  75                  80

Lys Asn Thr Val Asp Leu Thr Met Asn Asn Leu Glu Pro Glu Asp Thr
                85                  90                  95

Ala Val Tyr Tyr Cys Ala Ala Arg Asp Gly Ile Pro Thr Ser Arg Ser
            100                 105                 110

Val Glu Ser Tyr Asn Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser
        115                 120                 125

Ser
```

<210> 5

<211> 127

<212> PRT

<213> Lama glama

<400> 5

```
Gln Val Gln Leu Gln Asp Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Arg Thr Phe Ser Ala His
            20                  25                  30

Ser Val Tyr Thr Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg
        35                  40                  45

Glu Phe Val Ala Arg Ile Tyr Trp Ser Ser Ala Asn Thr Tyr Tyr Ala
    50                  55                  60

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
65                  70                  75                  80

Thr Val Asp Leu Leu Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val
                85                  90                  95

Tyr Tyr Cys Ala Ala Arg Asp Gly Ile Pro Thr Ser Arg Thr Val Gly
            100                 105                 110

Ser Tyr Asn Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
        115                 120                 125
```

<210> 6

<211> 124

<212> PRT

<213> Lama glama

<400> 6

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Phe Arg Val Asn
            20                  25                  30
```

```
Ala Met Gly Trp Tyr Arg Gln Val Pro Gly Asn Gln Arg Glu Phe Val
        35                  40                  45

Ala Ile Ile Thr Ser Ser Asp Thr Asn Asp Thr Thr Asn Tyr Ala Asp
    50                  55                  60

Ala Val Lys Gly Arg Phe Thr Ile Ser Thr Asp Asn Val Lys Lys Thr
65                  70                  75                  80

Val Tyr Leu Gln Met Asn Val Leu Lys Pro Glu Asp Thr Ala Val Tyr
                85                  90                  95

Tyr Cys Asn Ala Val Leu Gln Thr Ser Arg Trp Ser Ile Pro Ser Asn
            100                 105                 110

Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
        115                 120
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<210> 7

<211> 123

<212> PRT

<213> Lama glama

<400> 7

```
Gln Val Gln Leu Gln Asp Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Thr Thr Ser Gly Arg Thr Ile Ser Val Tyr
            20                  25                  30

Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
        35                  40                  45

Ala Ser Ile Ser Gly Ser Gly Ala Ile Thr Pro Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Asn Pro Glu Asp Thr Ala Val Tyr Tyr Cys
```

85 90 95

Ala Ala Ser Arg Tyr Ala Arg Tyr Arg Asp Val His Ala Tyr Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
115 120

<210> 8

<211> 124

<212> PRT

<213> Lama glama

<400> 8

Gln Val Gln Leu Gln Asp Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Thr Arg Thr Phe Ser Arg Tyr
20 25 30

Val Val Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
35 40 45

Ala Thr Ile Ser Trp Asn Gly Glu His Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Tyr Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr
65 70 75 80

Leu Gln Met Gly Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Ala Arg Ser Phe Trp Gly Tyr Asn Val Glu Gln Arg Asp Phe Gly
100 105 110

Ser Trp Gly Gln Gly Thr Pro Val Thr Val Ser Ser
115 120

<210> 9

<211> 120

<212> PRT

<213> Lama glama

<400> 9

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Phe Arg Val Asn
20 25 30

Ala Met Gly Trp Tyr Arg Gln Val Pro Gly Asn Gln Arg Glu Phe Val
35 40 45

Ala Ile Ile Thr Asn Asp Thr Thr Asn Tyr Ala Asp Ala Val Lys Gly
50 55 60

Arg Phe Thr Ile Ser Thr Asp Asn Val Lys Lys Thr Val Tyr Leu Gln
65 70 75 80

Met Asn Val Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn Thr
85 90 95

Val Leu Gln Thr Ser Arg Trp Asn Ile Pro Thr Asn Tyr Trp Gly Gln
100 105 110

Gly Thr Gln Val Thr Val Ser Ser
115 120

<210> 10

<211> 120

<212> PRT

<213> Lama glama

<400> 10

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Phe Arg Val Asn
            20                  25                  30

Ala Met Gly Trp Tyr Arg Gln Val Pro Gly Asn Gln Arg Glu Phe Val
        35                  40                  45

Ala Ile Ile Ser Gly Asp Thr Thr Asn Tyr Ala Asp Ala Val Lys Gly
    50                  55                  60

Arg Phe Thr Ile Ser Thr Asp Asn Val Lys Lys Thr Val Tyr Leu Gln
65                  70                  75                  80

Met Asn Val Leu Glu Ser Glu Asp Thr Ala Val Tyr Tyr Cys Asn Ala
                85                  90                  95

Val Leu Gln Thr Ser Arg Trp Ser Ile Pro Ser Asn Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Gln Val Thr Val Ser Ser
        115                 120
```

<210> 11

<211> 116

<212> PRT

<213> Lama glama

<400> 11

```
Gln Val Gln Leu Gln Asp Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ala Cys Val Ala Ser Gly Ser Ile Phe Ser Ile Asp
            20                  25                  30

Val Met Gly Trp Tyr Arg Gln Ala Pro Gly Gln Gln Arg Glu Leu Val
        35                  40                  45

Ala Thr Ile Thr Asn Ser Trp Thr Thr Asn Tyr Ala Asp Ser Val Lys
    50                  55                  60
```

```
Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Val Val Tyr Leu
65                  70                  75                  80

Gln Met Asn Ser Leu Lys Leu Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95

Ala Arg Arg Trp Tyr Gln Pro Glu Ala Trp Gly Gln Gly Thr Gln Val
            100                 105                 110

Thr Val Ser Ser
        115
```

<210> 12

<211> 115

<212> PRT

<213> Lama glama

<400> 12

```
Gln Val Gln Leu Gln Asp Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr His
            20                  25                  30

Trp Met Tyr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Thr Ile Asn Thr Asn Gly Leu Ile Thr Asp Tyr Ile His Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Lys Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Leu Asn Gln Ala Gly Leu Ser Arg Gly Gln Gly Thr Gln Val Thr
            100                 105                 110

Val Ser Ser
```

115

<210> 13

<211> 126

<212> PRT

<213> Lama glama

<400> 13

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Arg Thr Phe Ser Gly Tyr
            20                  25                  30

Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
        35                  40                  45

Ala Val Val Ser Gly Thr Gly Thr Ile Ala Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Glu Asn Thr Val Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Gly Leu Tyr Tyr Cys
                85                  90                  95

Ala Val Gly Pro Ser Ser Ser Arg Trp Tyr Tyr Arg Gly Ala Ser Leu
            100                 105                 110

Val Asp Tyr Trp Gly Lys Gly Thr Leu Val Thr Val Ser Ser
        115                 120                 125
```

<210> 14

<211> 123

<212> PRT

<213> Lama glama

<400> 14

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Glu Phe Glu Asn His
20 25 30

Trp Met Tyr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Thr Val Asn Thr Asn Gly Leu Ile Thr Arg Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Tyr Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Lys Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Lys Val Leu Pro Pro Tyr Ser Asp Asp Ser Arg Thr Asn Ala Asp
100 105 110

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
115 120

<210> 15

<211> 124

<212> PRT

<213> Lama glama

<400> 15

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Gly Thr Leu Ser Ser Tyr
20 25 30

Ile Thr Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
35 40 45

```
Gly Ala Val Ser Trp Ser Ser Ser Thr Ile Val Tyr Ala Asp Ser Val
    50                  55                  60

Glu Gly Arg Phe Thr Ile Ser Arg Asp Asn His Gln Asn Thr Val Tyr
65                  70                  75                  80

Leu Gln Met Asp Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Ala Arg Pro Tyr Gln Lys Tyr Asn Trp Ala Ser Ala Ser Tyr Asn
            100                 105                 110

Val Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
        115                 120
```

<210> 16

<211> 124

<212> PRT

<213> Lama glama

<400> 16

```
Gln Val Gln Leu Gln Asp Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Gly Thr Phe Ser Ser Ile
            20                  25                  30

Ile Met Ala Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
        35                  40                  45

Gly Ala Val Ser Trp Ser Gly Gly Thr Thr Val Tyr Ala Asp Ser Val
    50                  55                  60

Leu Gly Ar
```